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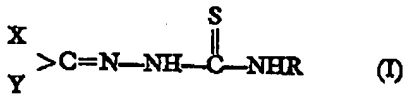
(54) NOVEL THIOSEMICARBAZONES, PROCESSES FOR THEIR PREPARATIONS, AND COMPOSITIONS INCORPORATING THEM

(71) We, STERLING-WINTHROP GROUP LIMITED, a British Company, of 12, Whitehall, London, S.W.1. do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns certain novel thiosemicarbazones, processes for their preparation, and compositions incorporatoig them.

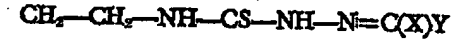
The novel thiosemicarbazones of this invention as hereinafter identified have been tested by standard chemotherapeutic evaluation procedures and found to have anti-microbial activity (a term used here to embrace not only anti-bacterial and anti-fungal but also anti-viral activities), and these compounds thus may be employed in human or veterinary medicine or in agricultural applications.

In one aspect of this invention there are therefore provided, as new compounds, the thiosemicarbazones which conform to the general formula:—



(I)

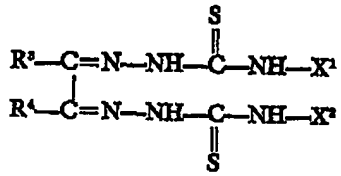
(wherein either X represents a carboxyl group, an alkyl group, or an unsubstituted aryl group, and Y represents an arylvinyl group, a carboxyalkyl group, a substituted or unsubstituted fluorenyl group, or the 4-R-thiosemicarbazone of a benzoyl group, or wherein X and Y together with the carbon atom between them, represent a substituted or unsubstituted fluoren-9-ylidene group, the tetraphenylcyclo-pentadienylidene group, the acenaphthen - 1 - on-2 - ylidene group, or an acenaphthen - 1 - one-(4 - R - thiosemicarbazone) - 2 - ylidene group; and in which R represents a hydrogen atom, or a substituted or unsubstituted aryl, alkyl, cycloalkyl or heterocyclic group, or when X and Y together with the carbon atom between the represent the fluoren - 9-ylidene group—represents a



group), and their non-toxic salts.

A few of the thiosemicarbazones of general formula I above are however already known, and to these we wish to make no claim. Accordingly, it should be noted that we make no claim herein to the following compounds namely:—

fluorenone thiosemicarbazone;
acenaphthenequinone mono - thiosemicarbazone;
benzylidene - acetone thiosemicarbazone;
benzylidene - acetone (4 - phenyl) - thiosemicarbazone;
and the bis(thiosemicarbazones) of the general formula:—



(II)

(wherein R^3 and R^4 are the same or different and each is a straight or branched alkyl group

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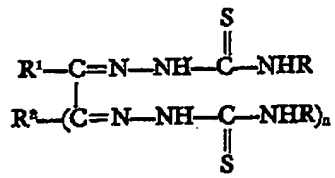
having from 1 to 10 carbon atoms, or is a phenyl group; and X^1 and X^2 are the same or different and each is a hydrogen atom, or is a straight or branched, saturated or unsaturated alkyl group having up to six carbon atoms) which have been described and claimed in British Patent No. 966,849.

The preferred compounds of general formula I above provided in accordance with this invention (subject to the foregoing disclaimer) are the thiosemicarbazones conforming to the following general formula:—

(III)



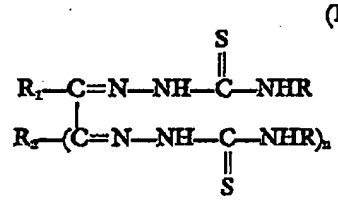
(wherein n is 0 or 1, and when n is 0, R^2 is then attached to the same carbon atom as R^1), then either R^1 represents a carboxyl group or an alkyl group and R^2 represents a styryl group, a carboxylalkyl group, or a substituted or unsubstituted 2-fluorenyl group or R^1 and R^2 together with the carbon atom between them represent a substituted or unsubstituted fluoren - 9- - ylidene group, the tetraphenyl*cyclo*pentadienylidene group, or the acenaphthen - 1 - one - 2-ylidene group, while when n is 1 then either R^1 and R^2 are both phenyl groups or together with the two conjoining carbon atoms between them they represent the acenaphthene - 1,2-bis - ylidene group and R represents a hydrogen atom or a substituted or unsubstituted aryl, alkyl or heterocyclic group, or

— when R^1 and R^2 together with the carbon atom(s) between them represent the fluoren-9 - ylidene group — represents a

group, and their non-toxic salts.

The most preferred compounds of general formula I above provided in accordance with this invention (subject still to the exclusion of fluorenone thiosemicarbazone and the benzil *bis*(thiosemicarbazones) disclosed in Patent No. 966,849) are the thiosemicarbazones of general formula:—

(IV)

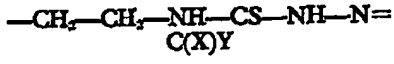


(wherein n is 0 or 1, and when n is 0 (R_2 is then attached to the same carbon atom as R_1) then R_1 represents a carboxyl group and R_2 is a carboxyalkyl group, or R_1 represents a methyl group and R_2 is the 2 - fluorenyl group or (provided that R is an optionally-substituted alkyl or *cyclo*alkyl radical with not more than 6 carbon atoms) the styryl group, or R_1 and R_2 together with the carbon atom between them, represent a substituted or unsubstituted fluoren - 9-ylidene group, the tetraphenyl*cyclo*pentadienylidene group, or (provided that R is not a hydrogen atom) an acenaphthene - 1 - on - 2-ylidene group, while

when n is 1 then R_1 and R_2 are both phenyl groups or together with the two conjoining carbon atoms between them they represent the acenaphthene - 1,2 - bis-ylidene group, and

R represents a hydrogen atom or a straight, branched, or *cyclo*alkyl group with not more than 6 carbon atoms or a substituted or unsubstituted phenyl, naphthyl, or pyridyl group, or—

when R_1 and R_2 together with the carbon atom(s) between them represents the fluoren-9-ylidene group—represents a



group) and their non toxic salts.

The new compounds of this invention herein identified when tested according to standard *in vitro* anti-bacterial and anti-fungal evaluation procedures possess anti-bacterial and anti-fungal activities, for instance against organisms such as *Staphylococcus aureus* and *Trichophyton mentagrophytes* at minimal growth inhibitory concentrations ranging from 5 to 100 mcg./ml. Specifically preferred new compounds of this invention displaying this anti-bacterial and/or anti-fungal activity include the following:—

Fluorenone 4 - methyl - thiosemicarbazone
Fluorenone 4 - ethyl - thiosemicarbazone
Fluorenone 4-*iso*propyl-thiosemicarbazone
Fluorenone 4-butyl-thiosemicarbazone
Fluorenone 4-*t*-butyl-thiosemicarbazone
Fluorenone 4-*cyclo*hexyl-thiosemicarbazone
Fluorenone 4-benzyl-thiosemicarbazone
Fluorenone 4-phenyl-thiosemicarbazone
Fluorenone 4-(2-methylphenyl)-thiosemicarbazone
Fluorenone 4 - (3-methylphenyl)-thiosemicarbazone
Fluorenone 4 - (4-methylphenyl)-thiosemicarbazone
Fluorenone 4 - (2 - methoxyphenyl) - thiosemicarbazone
Fluorenone 4 - (3-methoxyphenyl)-thiosemicarbazone
Fluorenone 4 - (4-methoxyphenyl)-thiosemicarbazone
Fluorenone 4 - (2-chlorophenyl)-thiosemicarbazone

Fluorenone 4 - (3-chlorophenyl)-thiosemicarbazone
Fluorenone 4 - (4-chlorophenyl)-thiosemicarbazone
Fluorenone 4 - (1-naphthyl)-thiosemicarbazone
Fluorenone 4-(2-pyridyl)-thiosemicarbazone
1,2-Ethylene bis - (fluorenone-4-thiosemicarbazone
3-Methyl-fluorenone thiosemicarbazone
1-Hydroxy-fluorenone thiosemicarbazone
2-Hydroxy-fluorenone thiosemicarbazone
4-Hydroxy-fluorenone thiosemicarbazone
1-Chloro-fluorenone thiosemicarbazone
2-Chloro-fluorenone thiosemicarbazone
4-Chloro-fluorenone thiosemicarbazone
2,7-Dichloro-fluorenone thiosemicarbazone
2-Bromo-fluorenone thiosemicarbazone
2,7-Dibromo-fluorenone thiosemicarbazone
2-Iodo-fluorenone thiosemicarbazone
2,7-Diiodo-fluorenone thiosemicarbazone
2-Nitro-fluorenone thiosemicarbazone
3-Nitro-fluorenone thiosemicarbazone
1-Carboxyl-fluorenone thiosemicarbazone
2-Carboxy-fluorenone thiosemicarbazone
4-Carboxy-fluorenone-thiosemicarbazone
1-Carbomethoxy-fluorenone thiosemicarbazone
2-Carbomethoxy-fluorenone thiosemicarbazone
4-Carbomethoxy-fluorenone thiosemicarbazone
1-Amino-fluorenone thiosemicarbazone
2-Amino-fluorenone thiosemicarbazone
4-Amino-fluorenone thiosemicarbazone
2-Amino-3-nitro-fluorenone thiosemicarbazone
1-Acetylamino-fluorenone thiosemicarbazone
2-Acetylamino-fluorenone thiosemicarbazone
4-Acetylamino-fluorenone thiosemicarbazone
2-Benzoylaminofluorenone thiosemicarbazone
1-Amido-fluorenone thiosemicarbazone
4-Amido-fluorenone thiosemicarbazone
1-Carboethoxyamino-fluorenone thiosemicarbazone
2-Carboethoxyamino-fluorenone thiosemicarbazone
2 - Carboethoxyamino - 3-nitro-fluorenone thiosemicarbazone
Tetraphenyl*cyclo*pentadienone thiosemicarbazone
Acenaphthenequinone di-thiosemicarbazone
Acenaphthenequinone mono-4-phenyl-thiosemicarbazone
Acenaphthenequinone mono-4-ethyl - thiosemicarbazone
Acenaphthenequinone bis - 4 - ethyl - thiosemicarbazone
Benzil *bis*-4-cyclohexyl-thiosemicarbazone
Benzil *bis*-4-phenyl-thiosemicarbazone
Benzil *bis*-4-benzyl-thiosemicarbazone
Benzil *bis*(4-(2-methylphenyl)-thiosemicarbazone
Benzil *bis*(4-(3-methylphenyl)-thiosemicarbazone
Benzil *bis*(4-(4-methylphenyl)-thiosemicarbazone
Benzil *bis*(4-(2-methoxyphenyl) - thiosemicarbazone
Benzil *bis*(4-(3-methoxyphenyl) - thiosemicarbazone
Benzil *bis*(4-(4-methoxyphenyl) - thiosemicarbazone
Benzil *bis*(4-(2-chlorophenyl) - thiosemicarbazone
Benzil *bis*(4-(3-chlorophenyl) - thiosemicarbazone
Benzil *bis*(4-(4-chlorophenyl) - thiosemicarbazone
Benzil *bis* 4-(1-naphthyl)-thiosemicarbazone
Benzil *bis*-4-(2-pyridyl)-thiosemicarbazone
Oxaloacetic acid thiosemicarbazone
2-Acetyl-fluorene thiosemicarbazone
Benzylidene-acetone 4-ethyl-thiosemicarbazone
Benzylidene-acetone 4 - *cyclo*hexyl - thiosemicarbazone
Benzylidene-acetone 4-benzyl-thiosemicarbazone

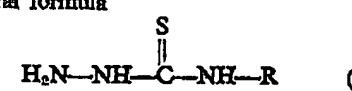
The determination of the quantitative and qualitative data pertaining to the anti-bacterial and/or anti-fungal activities of each individual compound can of course be readily performed using standard test procedure without any need for extensive experimentation by any ordinarily competent technician versed in such procedures.

The compounds of this invention herein identified can be prepared by any of the processes conventionally employed to make semicarbazones, in particular by reacting an appropriate ketone with an appropriate thiosemicarbazide, to yield directly both the 4-substituted and 4-unsubstituted compounds; while the former can also be prepared indirectly, by introducing the 4-substituent into the 4-unsubstituted compounds.

In another aspect this invention thus also provides processes for the preparation of the new thiosemicarbazones of general formula I above, in which a carbonyl compound of general formula:—

(V)

(where X and Y have the previously-indicated meanings) is reacted with a thiosemicarbazide of general formula



(VI)

(where R has the previously-indicated meaning) in a polar solvent and in the presence of

hydrogen ions to give the corresponding desired thiosemicarbazone of general formula I.

The two reagents should normally be employed in stoichiometric (thus equimolecular) amounts, except when a *bis* thiosemicarbazone is being prepared, when two moles of thiosemicarbazide are required for each mole of carbonyl compound.

The polar solvent employed is preferably an alcohol, such as ethanol; but other polar solvents can be used such as acetic acid or even water, and may in some cases give equally good or possibly better results.

Hydrogen ions must be present, but if one of the reagents or the polar solvent is already acidic (for instance if one employs the thiosemicarbazide hydrochloride as one of the reagents, or acetic acid as the polar solvent) then the inclusion of an additional source of hydrogen ions may be unnecessary. Where this is not the case, or simply as precaution, a source of hydrogen ions should be added to the reaction mixture, which most conveniently can be a mineral acid, such as hydrochloric acid.

This reaction is usually best effected at elevated temperatures, and often can most conveniently be performed at reflux of the polar solvent in which the reaction takes place.

While the process outlined above is that currently preferred for the direct preparation of at least most of the thiosemicarbazones of the invention, it should be apparent to any chemist that other direct methods of preparation may also be employed, and indeed that the compounds may also be prepared by indirect methods. Thus for instance it is possible to react an appropriate ketone with an appropriate amine to give a corresponding imino condensation product, and then to react the latter with thiosemicarbazide, in aqueous acid solution, to give the desired semicarbazone.

The invention of course extends to the thiosemicarbazones of general formulae I, III and IV above, subject to the exclusion of the previously specified known compounds, whenever produced by any of the processes herein described.

It is convenient at this point to note that two of the substituted fluorenone compounds used as starting materials for the processes outlined above, namely 1 - carboethoxy - aminofluorenone and 4 - acetamido - fluorenone, are themselves novel compounds. The preparation of these novel starting materials is described subsequently, and this invention also extends to them *per se*, to the processes for their preparation described herein, and to the compounds when thus prepared.

The compounds of general formulae I, III and IV provided by this invention, whether prepared in the manner described herein or not, exhibit a marked anti-microbial activity *in vitro* and although the compounds have not yet been subjected to full-scale clinical trials it appears from animal tests that this anti-microbial activity is also displaced *in vivo*. As would be expected, the activities of the various compounds vary, not only according to the compound used but also dependent on the micro-organism under test. However it can in general be said that the compounds of the invention possess varying degrees of useful bacterial and/or fungicidal and/or virucidal activity. They are therefore capable of employment as disinfectants generally, and more specifically in human and veterinary medicine, that is to say in the treatment of infections of microbial origin in animals including man.

However, before any of the compounds of this invention may be used in human or veterinary medicine, they should preferably be formed into pharmaceutical compositions by association with suitable pharmaceutical vehicles.

The term "pharmaceutical" is used herein to exclude any possibility that the nature of the vehicle, considered of course in relation to the route by which the composition is intended to be administered, could be harmful rather than beneficial. The choice of a suitable mode of presentation, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

Accordingly, in yet another aspect, this invention also provides pharmaceutical compositions containing as their anti-microbial active ingredient one or more of the thiosemicarbazones of general formula I, III or IV above (subject to the previously-expressed exclusions) in association with a suitable pharmaceutical vehicle.

The compositions of this invention may be administered topically, orally, sublingually, transcutaneously, rectally or vaginally, and in in respect of these modes, the "pharmaceutical vehicle" is preferably:—

a) the pulverulent solid, usually inert, diluent of a dusting powder or the pasty or semi-liquid oil/water or water/oil emulsion of a cream, lotion, or salve;
b) the ingestible excipient of a tablet, coated tablet, sublingual tablet or pill; the ingestible container of a capsule or sachet; the ingestible pulverulent solid carrier of a powder; or the ingestible liquid medium of a syrup, solution, suspension or elixir.
c) a sterile injectable liquid solution or suspension medium.
d/e) a base material of low melting point capable of releasing the active ingredient to perform its anti-microbial function, which base material when appropriately shaped forms a suppository or pessary.

Whilst the modes of presentation just listed

represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The relative and absolute amounts of the anti-microbial active ingredient(s) in the compositions of this invention may be varied widely dependent on the function they are intended to fulfill in the composition, and the purposes to which the compositions may be put are so various that it is thought that no worthwhile general guidance on this point can usefully be given. However, anyone accustomed to the formulation of pharmaceutical compositions can safely and easily employ the anti-microbial active ingredients of this invention in accordance with his knowledge and experience.

In order that the invention may be still better understood it will now be described in more detail, though only by way of illustration, first in the following Examples which show details of recommended methods for the preparation of certain preferred compounds, and secondly in the subsequent test reports which demonstrate the anti-microbial activity of some of these compounds:—

Methods for Preparation of Substituted Fluorenone Thiosemicarbazones

Example 1:
Preparation of 3-Methyl - fluorenone thiosemicarbazone

Equimolecular quantities (0.01 mole each) of thiosemicarbazide and of 3 - methyl-fluorenone are dissolved in 95% ethanol (Industrial Methylated Spirits) containing 3—4 drops of concentrated hydrochloric acid. The solution is heated to reflux and maintained there until the reaction is complete, usually for ½—2 hours. The desired product tends to separate out during the course of the reaction, and after cooling the reaction mixture can then be filtered off and isolated. If however the desired product fails to crystallize out after cooling, the volume of the reaction mixture is reduced under vacuum until the desired product separates. Yield=85%. Purification by recrystallization from methanol gives the desired 3 - methyl - fluorenone thiosemicarbazone, m. pt.=235°C (dec.).

Other compounds were prepared in a generally analogous manner, using equimolecular amounts of the appropriate reagents and refluxing them in suitable solvents (usually Industrial Methylated Spirits) until the reaction was virtually complete, and recrystallizing the product from the solvents indicated in the following summary:—

Example	Compound Prepared	Recrystallization Solvent	Yield %	Melting point °C.
19	2-Carbomethoxy-fluorenone thiosemicarbazone	Glacial acetic acid	95	220(dec.)
20	4-Carbomethoxy-fluorenone thiosemicarbazone	Ethanol/Benzene (1:1)	98	226—227
21	1-Amino-fluorenone thiosemicarbazone	Methanol	40	192
22	2-Amino-fluorenone thiosemicarbazone	*n*-Butanol	40	217(dec.)
23	4-Amino-fluorenone thiosemicarbazone	Glacial acetic acid	80	225
24	2-Amino-3-nitro-fluorenone thiosemicarbazone	Dimethylformamide (75%)	75	275(dec.)
25	1-Acetylamino-fluorenone thiosemicarbazone	Ethanol	50	225(dec.)
26	2-Acetylamino-fluorenone thiosemicarbazone	*n*-Butanol	80	255—258(dec.)
27	4-Acetylamino-fluorenone thiosemicarbazone	Ethanol	75	274
28	2-Benzoylamino-fluorenone thiosemicarbazone	Ethanol	90	250(dec.)
29	1-Amido-fluorenone thiosemicarbazone	Ethanol	99.5	257(dec.)
30	4-Amido-fluorenone thiosemicarbazone	Ethanol	90	245(dec.)
31	1-Carbethoxyamino-fluorenone thiosemicarbazone	Ethanol	90	208(dec.)
32	2-Carboethoxyamino-fluorenone thiosemicarbazone	Glacial acetic acid	90	243(dec.)
33	2-Carboethoxyamino-3-nitro-fluorenone thiosemicarbazone	Dimethylformamide (75%)	90	238(dec.)

Notes: 1. Ethanol refers to I.M.S. (Industrial Methylated Spirits).
2. The starting material for Example 31 was prepared as described in Example A subsequently.
3. The starting material for Example 27 was prepared as described in Example B subsequently.

It was established during these preparations that in general glacial acetic acid and dimethylformamide are less suitable as solvents for use in these procedures than the alcohols.

It is of interest that in the preparation of 2-amino fluorenone thiosemicarbazone, during the course of the reaction between 2 - aminofluorenone and thiosemicarbazide in 95% ethanol (I.M.S.) under reflux, an orange-coloured product (Dec. 217°C) separated out. This orange product was then dissolved in *n*-butanol and the solution filtered. When the filtrate was allowed to stand for 6—7 days at room temperature, the product (Dec. 217°C, m. pt.= 227°C) crystallized out in the form of red needles. However, when the volume of the *n*-butanol solution was reduced under vacuum without allowing it to stand for a few days, the orange product was again obtained. The infra-red spectra of both compounds were identical.

Methods of Preparation of Fluorenone 4-Substituted Thiosemicarbazones

Example 34:

Preparation of fluorenone 4 - methyl-thiosemicarbazone

Equimolecular quantities (0.02 mole each) of fluorenone and 4 - methyl - thiosemicarbazide are dissolved in 95% ethanol (I.M.S.) containing 4—5 drops of concentrated hydrochloric acid. The solution is heated to reflux and maintained there until the reaction is complete, usually after 20—30 minutes. The desired product should separate during the course of the reaction, and after cooling the reaction mixture can then be filtered off and isolated. Yield=95%. Purification by recrystallization from ethanol gives the desired fluorenone 4-methyl - thiosemicarbazone, m. pt.=149°C.

Other compounds were prepared in a generally similar manner, using equimolecular amounts of the appropriate reagents and refluxing them in suitable solvents (usually Industrial Methylated Spirits) until the reaction was virtually complete, and recrystallizing the product from the solvents indicated in the following summary:—

Example	Compound Prepared	Recrystallization Solvent	Yield %	Melting point °C.
35	Fluorenone 4-ethyl-thiosemicarbazone	Methanol	80	142—143(dec.)
36	Fluorenone 4-*iso*propyl-thiosemicarbazone	Benzene/Petroleum Ether (1:1)	90	167—168(dec.)
37	Fluorenone 4-butyl-thiosemicarbazone	Methanol	97	97
38	Fluorenone 4-*tert*.butyl-thiosemicarbazone	Ethanol	80	183.5—184.5(dec.)
39	Fluorenone 4-*cyclo*hexyl-thiosemicarbazone	Ethanol	90	180—181(dec.)
40	Fluorenone 4-phenyl-thiosemicarbazone	*n*-Butanol	90	197—198

Example	Compound Prepared	Recrystallization Solvent	Yield %	Melting point °C.
41	Fluorenone 4-benzyl-thiosemicarbazone	Ethanol	90	170—171(dec.)
42	Fluorenone 4-(2-methylphenyl)-thiosemicarbazone	Ethanol	88	206—207
43	Fluorenone 4-(3-methylphenyl)-thiosemicarbazone	Ethanol	90	190(dec.)
44	Fluorenone 4-(4-methylphenyl)-thiosemicarbazone	Ethanol	92	216(dec.)
45	Fluorenone 4-(2-methoxyphenyl)-thiosemicarbazone	Ethanol	90	198(dec.)
46	Fluorenone 4-(3-methoxyphenyl)-thiosemicarbazone	Ethanol	80	193
47	Fluorenone 4-(4-methoxyphenyl)-thiosemicarbazone	Ethanol	80	192
48	Fluorenone 4-(2-chlorophenyl)-thiosemicarbazone	Ethanol	60	220—221(dec.)
49	Fluorenone 4-(3-chlorophenyl)-thiosemicarbazone	Ethanol	70	191—192(dec.)
50	Fluorenone 4-(4-chlorophenyl)-thiosemicarbazone	Ethanol	90	224(dec.)
51	Fluorenone 4-(1-naphthyl)-thiosemicarbazone	Dimethyl oxalate	90	230—231(dec.)
52	Fluorenone 4-(2-pyridyl)-thiosemicarbazone	Benzene	95	118—119

[Note: Ethanol refers to I.M.S.]

Example 53:

Preparation of 1,2 - ethylene - bis (fluorenone-4 - thiosemicarbazone)

Ethylene bis-thiosemicarbazide (0.01 mole) was dissolved in 100 ml. of 95 ethanol (I.M.S.) containing 3 ml. of concentrated hydrochloric acid. Fluorenone (0.02 mole) was added to the solution and the mixture refluxed for half an hour. The reaction product precipitated out during the course of the reaction and, after cooling the reaction mixture, this product was filtered off and recrystallized from 80% alcoholic dimethylformamide. The compound was found to be practically insoluble in all common organic solvents. Yield 60%, m. p.t= 260°C (dec.).

Method for Preparation of Benzil Bis(4-Substituted Thiosemicarbazones).

Example 54:

Preparation of Benzil bis - 4 - *cyclo*hexyl-thiosemicarbazone

Benzil (0.01 mole) and 4 - *cyclo*hexyl-thiosemicarbazide (0.02 mole) were dissolved in 50 ml. of warm 95% ethanol (I.M.S.) containing a few drops of concentrated hydrochloric acid. The mixture was refluxed for 1—2 hours, and during the course of the reaction the product separated out. After cooling the reaction mixture, the product was filtered off and recrystallized from 80—85% dimethylformamide until pure. An 80% yield of the desired benzil *bis* - *cyclo*hexyl - thiosemicarbazone was thus obtained, m. pt.= 245°C (dec.).

Example	Compound	Yield %	Melting point °C.
55	Benzil *bis*-4-phenyl-thiosemicarbazone	50	223—224
56	Benzil *bis*-4-benzyl-thiosemicarbazone	80	238(dec.)
57	Benzil *bis*(4-(2-methylphenyl)-thiosemicarbazone)	65	226(dec.)
58	Benzil *bis*(4-(3-methylphenyl)-thiosemicarbazone)	65	222(dec.)
59	Benzil *bis*(4-(4-methylphenyl)-thiosemicarbazone)	65	210(dec.)
60	Benzil *bis*(4-(2-methoxyphenyl)-thiosemicarbazone	65	216(dec.)
61	Benzil *bis*(4-(3-methoxyphenyl)-thiosemicarbazone)	30	223(dec.)
62	Benzil *bis*(4-(4-methoxyphenyl)-thiosemicarbazone)	40	221(dec.)
63	Benzil *bis*(4-(2-chlorophenyl)-thiosemicarbazone)	20	218
64	Benzil *bis*(4-(3-chlorophenyl)-thiosemi-carbazone)	40	233(dec.)
65	Benzil *bis*(4-(4-chlorophenyl)-thiosemicarbazone)	45	242
66	Benzil *bis*(4-(1-naphthyl)-thiosemicarbazone)	50	284
67	Benzil *bis*(4-(2-pyridyl)-thiosemicarbazone)	80	237(dec.)

Example 68:
Preparation of tetraphenyl*cyclo*pentadienone thiosemicarbazone

Tetraphenyl*cyclo*pentadienone (0.01 mole) was dissolved in 700 ml. of 95% ethanol (I.M.S.), containing 2—3 drops of concentrated hydrochloric acid. Thiosemicarbazide (0.01 mole) was then added to the solution and the mixture refluxed for 8 days. The volume of the solution was then reduced to 350 ml. and, on cooling the solution, the product separated out. The solid was then filtered off, dissolved in the minimum volume of chloroform, and the solution filtered. 100 ml. of 95% ethanol (I.M.S.) was added to the filtrate and the chloroform distilled off. Upon cooling the ethanolic solution, dark red needles crystallized out. Yield 95%. M. pt.=242°C (dec.).

Example 69:
Preparation of acenaphthenequinone di-thiosemicarbazone

Acenaphthenequinone (3.6 g.) was dissolved in a mixture of benzene (200 ml.) and *n*-butanol (300 ml.). Thiosemicarbazide (4 g.) was dissolved in 20 ml. of water containing 1 ml. of concentrated hydrochloric acid and this was added to the hot solution of acenaphthenequinone. The mixture was refluxed for 16 hours and the product precipitated out during the course of the reaction. Before the mixture had cooled, the product was filtered off, extracted twice with hot water and once with chloroform, and finally recrystallized from dilute dimethylformamide to give small yellow needles. Yield 40%. M. pt.=253—254°C.

Example 70:
Preparation of acenaphthenequinone mono-(4-phenyl)-thiosemicarbazone

Equimolecular quantities (0.02 mole) of acenaphthenequinone and thiosemicarbazide were refluxed, in a mixture of 95% ethanol (I.M.S.) (600 ml.) and benzene (150 ml.) containing 4 drops of concentrated hydrochloric acid, for one hour. The volume of the solution was then reduced to 300 ml. and the product precipitated out. The product was filtered off and recrystallized from *n*-butanol. Yield 80%. M. pt.=193—194°C (dec.)

Example 71:
Preparation of acenaphthenequinone mono-(4-ethyl) - thiosemicarbazone

Equimolecular quantities (0.01 mole) of acenaphthenequinone and 4 - ethyl - thiosemicarbazide were refluxed in a mixture of dimethyl - formamide (100 ml.) and 95% ethanol (I.M.S.) (150 ml.), containing 3 drops of concentrated hydrochloric acid, for one hour. The product was precipitated from the reaction mixture by the addition of 100 ml. of 95% ethanol (I.M.S.). The solid was then filtered off and recrystallized from *n*-butanol to give fine light yellow needles. Yield 55%. M. pt.=219°C (dec.)

Example 72:
Preparation of acenaphthenequinone bis - 4-ethyl - thiosemicarbazone

The same procedure was used as in Example 71, except that twice the quantity (0.02 mole) of 4 - ethyl - thiosemicarbazide was employed and the mixture was refluxed for five hours. Yield 80%. M. pt.=230°C (dec.).

Methods for Preparation of Benzylidene Acetone 4-substituted Thiosemicarbazones

Example 73:
Preparation of benzylidene - acetone 4 - ethyl-thiosemicarbazones

Equimolecular quantities (0.01 mole) of benzylidene - acetone and 4 - ethyl - thiosemicarbazide were refluxed for one hour in 25 ml. of methanol containing 2—3 drops of concentrated hydrochloric acid. The reaction mixture was then filtered and the filtrate cooled in an ice-salt bath for 12—15 hours. The product failed to crystallize out from the cold reaction mixture and so the solution was evaporated to dryness. The residue was taken up in benzene and the product was precipitated out by the addition of excess petroleum ether. The product was filtered off and recrystallized from a 40:60 mixture of benzene and petroleum ether. Yield 90%. M. pt.=89°C.

Other compounds were prepared in a similar manner, except that the product crystallized out from the cold reaction mixture, was filtered off and recrystallized from methanol until pure. The results were as follows:—

Example	Compound Prepared	Yield %	Melting Point °C
74	Benzylidene-acetone 4-*cyclo*hexylthiosemicarbazone	95	186
75	Benzylidene-acetone 4-benzyl-thiosemicarbazone	90	130

Example 68:
Preparation of tetraphenyl*cyclo*pentadienone thiosemicarbazone

Tetraphenyl*cyclo*pentadienone (0.01 mole) was dissolved in 700 ml. of 95% ethanol (I.M.S.), containing 2—3 drops of concentrated hydrochloric acid. Thiosemicarbazide (0.01 mole) was then added to the solution and the mixture refluxed for 8 days. The volume of the solution was then reduced to 350 ml. and, on cooling the solution, the product separated out. The solid was then filtered off, dissolved in the minimum volume of chloroform, and the solution filtered. 100 ml. of 95% ethanol (I.M.S.) was added to the filtrate and the chloroform distilled off. Upon cooling the ethanolic solution, dark red needles crystallized out. Yield 95%. M. pt.=242°C (dec.).

Example 69:
Preparation of acenaphthenequinone dithiosemicarbazone

Acenaphthenequinone (3.6 g.) was dissolved in a mixture of benzene (200 ml.) and *n*-butanol (300 ml.). Thiosemicarbazide (4 g.) was dissolved in 20 ml. of water containing 1 ml. of concentrated hydrochloric acid and this was added to the hot solution of acenaphthenequinone. The mixture was refluxed for 16 hours and the product precipitated out during the course of the reaction. Before the mixture had cooled, the product was filtered off, extracted twice with hot water and once with chloroform, and finally recrystallized from dilute dimethylformamide to give small yellow needles. Yield 40%. M. pt.=253—254°C.

Example 70:
Preparation of acenaphthenequinone mono-(4-phenyl)-thiosemicarbazone

Equimolecular quantities (0.02 mole) of acenaphthenequinone and thiosemicarbazide were refluxed, in a mixture of 95% ethanol (I.M.S.) (600 ml.) and benzene (150 ml.) containing 4 drops of concentrated hydrochloric acid, for one hour. The volume of the solution was then reduced to 300 ml. and the product precipitated out. The product was filtered off and recrystallized from *n*-butanol. Yield 80%. M. pt.=193—194°C (dec.)

Example 71:
Preparation of acenaphthenequinone mono-(4-ethyl) - thiosemicarbazone

Equimolecular quantities (0.01 mole) of acenaphthenequinone and 4 - ethyl - thiosemicarbazide were refluxed in a mixture of dimethyl - formamide (100 ml.) and 95% ethanol (I.M.S.) (150 ml.), containing 3 drops of concentrated hydrochloric acid, for one hour. The product was precipitated from the reaction mixture by the addition of 100 ml. of 95% ethanol (I.M.S.). The solid was then filtered off and recrystallized from *n*-butanol to give fine light yellow needles. Yield 55%. M. pt.=219°C (dec.)

Example 72:
Preparation of acenaphthenequinone bis - 4-ethyl - thiosemicarbazone

The same procedure was used as in Example 71, except that twice the quantity (0.02 mole) of 4 - ethyl - thiosemicarbazide was employed and the mixture was refluxed for five hours. Yield 80%. M. pt.=230°C (dec.).

Methods for Preparation of Benzylidene Acetone 4-substituted Thiosemicarbazones

Example 73:
Preparation of benzylidene - acetone 4 - ethyl-thiosemicarbazones

Equimolecular quantities (0.01 mole) of benzylidene - acetone and 4 - ethyl - thiosemicarbazide were refluxed for one hour in 25 ml. of methanol containing 2—3 drops of concentrated hydrochloric acid. The reaction mixture was then filtered and the filtrate cooled in an ice-salt bath for 12—15 hours. The product failed to crystallize out from the cold reaction mixture and so the solution was evaporated to dryness. The residue was taken up in benzene and the product was precipitated out by the addition of excess petroleum ether. The product was filtered off and recrystallized from a 40:60 mixture of benzene and petroleum ether. Yield 90%. M. pt.=89°C.

Other compounds were prepared in a similar manner, except that the product crystallized out from the cold reaction mixture, was filtered off and recrystallized from methanol until pure. The results were as follows:—

Example	Compound Prepared	Yield %	Melting Point °C
74	Benzylidene-acetone 4-*cyclo*hexylthiosemicarbazone	95	186
75	Benzylidene-acetone 4-benzyl-thiosemicarbazone	90	130

Example 76:
Preparation of oxaloacetic acid thiosemicarbazone

Oxaloacetic acid (0.1 mole) was added to a solution of thiosemicarbazide (0.1 mole) in 50 ml. of hot water. The mixture was kept warm for 30 minutes and then allowed to cool. The product precipitated out and was filtered off and recrystallized from water. Yield 75%. M. pt.=199—200°C.

Example 77:
Preparation of 2 - acetyl - fluorenone thiosemicarbazone

The same procedure was used as in Example 1, but employing equimolecular quantities of 2 - acetyl - fluorene and thiosemicarbazide. The product was recrystallized from ethanol. Yield 95%. M. pt.=204°C.

Preparation of Starting Material

Example A:
Preparation of 1 - carboethoxyamino-fluorenone

1 - Amino - fluorenone (5 g.) was dissolved in dry pyridine (25 ml.) and the solution was cooled in an ice-salt bath. Ethyl chloroformate (5 ml.) was added dropwise to the cold solution and the mixture was kept well stirred throughout the addition. The solution was allowed to stand for 3 hours, and then water (200 ml.) was added to precipitate the product. The solid was filtered off and recrystallized twice from methanol to give fine yellow needles. Yield 75%. M. pt.=104°C.

Example B:
Preparation of 4 - acetylamino - fluorenone

4 - Amino - fluorenone (2 g.) was dissolved in glacial acetic acid (10 ml.) and redistilled acetic anhydride (2 ml.) was added to the solution. The mixture was refluxed for 15 minutes and allowed to cool. The product was precipitated by the addition of water (100 ml.), the solid filtered off and recrystallized twice from ethanol to give fine yellow needles. Yield: 80%. M. pt.=295°C.

In order to demonstrate the anti-microbial activity of the thiosemicarbazones of this invention the results of certain evaluations will now be given below:—

Evaluation I:
Antimicrobial (antifungal, antibacterial) Activity.

The following compounds display a minimal growth inhibitory concentration of 50 mcg/ml. or less:—

Compound	Organism	MIC (mcg/ml)
4-chloro-fluorenenone thiosemicarbazone	S. aureus	3.9
4-hydroxy-fluorenone thiosemicarbazone	S. aureus	31.3
Benzylidene-acetone 4-ethyl-thiosemicarbazone	T. menta	25.0
Benzylidene-acetone 4-phenyl-thiosemicarbazone	T. menta.	50.0
2-hydroxy-fluoreneone thiosemicarbazone	S. aureus	7.8
Benzil bis-4-phenyl-thiosemicarbazone	S. aureus	12.5
1-amino-fluorenone thiosemicarbazone	S. aureus	31.3
	T. menta.	31.3
2-carbethoxyamino-fluorenenone thiosemi carbazone	S. aureus	15.6
1-hydroxy-fluorenone thiosemicarbazone	S. aureus	3.9
3-methyl-fluorenone thiosemicarbazone	S. aureus	7.8

The following other compounds have also shown promising activity:—

2 - Benzoylamino - fluorenone thiosemicarbazone
Fluorenone 4 - (2 - pyridyl) - thiosemicarbazone
2,7 - Dichloro - fluorenone thiosemicarbazone
2 - Iodo - fluorenone thiosemicarbazone
Benzil *bis* - 4 - (2 - tolyl) - thiosemicarbazone
Benzil *bis* - 4 - (3 - tolyl) - thiosemicarbazone
Benzil *bis* - 4 - (4 - tolyl) - thiosemicarbazone
Benbil *bis* - 4 - benzyl - thiosemicarbazone
Benzil *bis* - 4 - (*cyclo*hexyl) - thiosemicarbazone
Acenaphthenequinone mono - 4 - (phenyl)-thiosemicarbazone
Benzylidene - acetone - 4 - *cyclo*hexyl-thiosemicarbazone
Benzylidene - acetone 4 - benzyl - thiosemicarbazone

Evaluation II:

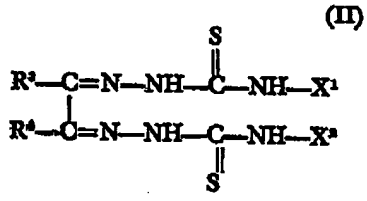
Antiviral Activity

	Intra-peritoneal Influenza Virus	Intra-peritoneal Vaccinia Virus
2-Nitro-fluorenone thiosemicarbazone	200	766
2-Amino-fluorenone thiosemicarbazone	200	1055
2-Chloro-fluoreneone thiosemicarbazone	200	1055
2-Iodo-fluorenenone thiosemicarbazone	400	—
4-Amino-fluorenone thiosemicarbazone	80	—
Tetraphenyl*cyclo*pentadienyl thiosemicarbazone	40	—
Acenaphthenequinone dithiosemicarbazone	200	—

We disclaim the following known compounds

fluorenone thiosemicarbazone;
acenaphthenequinone mono-thiosemicarbazone;
benzylidene - acetone thiosemicarbazone;
benzylidene - acetone (4 - phenyl) - thiosemicarbazone;
and
the benzil bis(thiosemicarbazones) of the general formula:—

(II)

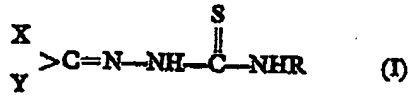


(wherein R^3 and R^4 are the same or different and each is a straight or branched alkyl group having from 1 to 10 carbon atoms, or is a phenyl group; and X^1 and X^2 are the same or different and each is a hydrogen atom, or is a straight or branched, saturated or unsaturated alkyl group having up to six carbon atoms) which have been described and claimed in British Patent No. 966,849.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. Thiosemicarbazones which conform to the general formula:—



(I)

(wherein either X represents a carboxyl group, an alkyl group, or an unsubstituted aryl group, and Y represents an arylvinyl group, a carboxyalkyl group, a substituted or unsubstituted fluorenyl group or the 4-R-thiosemicarbazone of a benzoyl group, or wherein X and Y together with the intervening carbon atom, represent a substituted or unsubstituted fluoren - 9 - ylidene group, the tetraphenyl-*cyclo*pentadienylidene group, the acenaphthen-1 - on - 2 - ylidene group, or an acenaphthen-1 - one - (4 - R - thiosemicarbazone) - 2-ylidene group; and in which R represents a

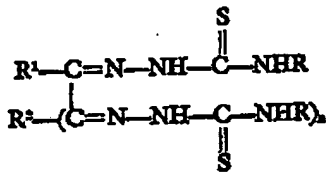
hydrogen atom, or a substituted or unsubstituted aryl, *cyclo*alkyl, alkyl or heterocyclic group, or—when X and Y together with the carbon atom between them represent the fluoren - 9 - ylidene group—represents a

$$-CH_2-CH_2-NH-CS-NH-N=C(X)Y$$

group), and their non-toxic salts.

2. Thiosemicarbazones as claimed in claim 1, which conform to the general formula:—

(III)



(wherein n is 0 or 1, and

when n is 0 (R^2 is then attached to the same carbon atom as R^1) then either R^1 represents a carboxyl group or an alkyl group and R^2 represents a styryl group, a carboxylalkyl group, or a substituted or unsubstituted 2-fluorenyl group, or R^1 and R^2 together with the carbon atom between them represent a substituted or unsubstituted fluoren - 9 - ylidene group, the tetraphenyl*cyclo*pentadienylidene group, or the acenaphthen - 1 - on-2 - ylidene group, while

when n is 1, then either R^1 and R^2 are both phenyl groups or together with the two conjoining carbon atoms between them they represent the acenaphthene - 1,2 - bis - ylidene group

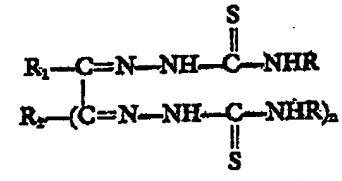
and R represents a hydrogen atom or a substituted or unsubstituted aryl, alkyl or heterocyclic group, or—when R^1 and R^2 together with the carbon atom(s) between them represent the fluoren - 9 - ylidene group—represents a

$$-CH_2-CH_2-NH-CS-NH-N=C(X)Y$$

group), and their non-toxic salts.

3. Thiosemicarbazones as claimed in claim 1 or claim 2, which conform to the general formula:—

(IV)



(wherein n is 0 or 1, and

when n is 0, (R_2 is then attached to the same carbon atom as R_1), then R_1 represents a carboxyl group and R_2 is a carboxyalkyl group, or R_1 represents a methyl group and R_2 is the 2 - fluorenyl group or (provided that R is an optionally-substituted alkyl or *cyclo*alkyl radical with not more than 6 carbon atoms) the styryl group, or R_1 and R_2 together with the carbon atom between them represent a substituted or unsubstituted fluoren - 9 - ylidene group, the tetraphenyl*cyclo*pentadienylidene group, or (provided that R is not a hydrogen atom) an acenaphthen - 1 - on - 2 - ylidene group, while

when n is 1, then R_1 and R_2 are both phenyl groups or together with the two conjoining carbon atoms between them they represent the acenaphthene - 1,2 - bis - ylidene group and

R represents a hydrogen atom or a straight, branched or cyclic alkyl group with not more than 6 carbon atoms or a substituted or unsubstituted phenyl, naphthyl or pyridyl group, or—when R_1 and R_2 together with the carbon atom(s) between them represent the fluoren-9 - ylidene group—represents a

$$-CH_2-CH_2-NH-CS-NH-N=C(X)Y$$

group), and their non-toxic salts.

4. Fluorenone 4 - methyl - thiosemicarbazone.

5. Fluorenone 4 - ethyl - thiosemicarbazone.

6. Fluorenone 4 - *iso*propyl - thiosemicarbazone.

7. Fluoroenone 4 - butyl - thiosemicarbazone.

8. Fluorenone 4 - *t* - butyl - thiosemicarbazone.

9. Fluorenone 4 - *cyclo*hexyl - thiosemicarbazone.

10. Fluorenone - 4 - benzyl - thiosemicarbazone.

11. Fluorenone 4 - phenyl - thiosemicarbazone.

12. Fluorenone 4 - (2 - methylphenyl)-thiosemicarbazone.

13. Fluorenone 4 - (3 - methylphenyl)-thiosemicarbazone.

14. Fluorenone 4 - (4 - methylphenyl)-thiosemicarbazone.

15. Fluorenone 4 - (2 - methoxyphenyl)-thiosemicarbazone.

16. Fluorenone 4 - (3 - methoxyphenyl)-thiosemicarbazone.

17. Fluorenone 4 - (4 - methoxyphenyl)-thiosemicarbazone.

18. Fluorenone 4 - (2 - chlorophenyl)-thiosemicarbazone.

19. Fluorenone 4 - (3 - chlorophenyl)-thiosemicarbazone.

20. Fluorenone 4 - (4 - chlorophenyl)-thiosemicarbazone.

21. Fluorenone 4 - (1 - naphthyl) - thiosemicarbazone.

22. Fluorenone 4 - (2 - pyridyl) - thiosemicarbazone.
23. 1,2 - Ethylene - bis - (fluorenone - 4-thiosemicarbazone).
24. 3 - Methyl - fluorenone thiosemicarbazone.
25. 1 - Hydroxy - fluorenone thiosemicarbazone.
26. 2 - Hydroxy - fluorenone thiosemicarbazone.
27. 4 - Hydroxy - fluorenone thiosemicarbazone.
28. 1 - Chloro - fluorenone thiosemicarbazone.
29. 2 - Chloro - fluorenone thiosemicarbazone.
30. 4 - Chloro - fluorenone thiosemicarbazone.
31. 2,7 - Dichloro - fluorenone thiosemicarbazone.
32. 2 - Bromo - fluorenone thiosemicarbazone.
33. 2,7 - Dibromo - fluorenone thiosemicarbazone.
34. 2 - Iodo - fluorenone thiosemicarbazone.
35. 2,7 - Diiodo - fluorenone thiosemicarbazone.
36. 2 - Nitro - fluorenone thiosemicarbazone.
37. 3 - Nitro - fluorenone thiosemicarbazone.
38. 1 - Carboxy - fluorenone thiosemicarbazone.
39. 2 - Carboxy - fluorenone thiosemicarbazone.
40. 4 - Carboxy - fluorenone thiosemicarbazone.
41. 1 - Carbomethoxy - fluorenone thiosemicarbazone.
42. 2 - Carbomethoxy - fluorenone thiosemicarbazone.
43. 4 - Carbomethoxy - fluorenone thiosemicarbazone.
44. 1 - Amino - fluorenone thiosemicarbazone.
45. 2 - Amino - fluorenone thiosemicarbazone.
46. 4 - Amino - fluorenone thiosemicarbazone.
47. 2 - Amino - 3 - nitro - fluorenone thiosemicarbazone.
48. 2 - Acetylamino - fluorenone thiosemicarbazone.
49. 2 - Acetylamino - fluorenone thiosemicarbazone.
50. 4 - Acetylamino - fluorenone thiosemicarbazone.
51. 2 - Benzoylamino - fluorenone thiosemicarbazone.
52. 1 - Amido - fluorenone thiosemicarbazone.
53. 4 - Amido - fluorenone thiosemicarbazone.
54. 1 - Carboethoxyamino - fluorenone thiosemicarbazone.
55. 2 - Carboethoxyamino - fluorenone thiosemicarbazone.
56. 2 - Carboethoxyamino - 3 - nitrofluorenone thiosemicarbazone.
57. Tetraphenyl*cyclo*pentadienone thiosemicarbazone.
58. Acenaphthenequinone di - thiosemicarbazone.
59. Acenaphthenequinone mono - (4 - phenyl - thiosemicarbazone).
60. Acenaphthenequinone mono - (4 - ethyl-thiosemicarbazone).
61. Acenaphthenequinone *bis* - (4 - ethyl-thiosemicarbazone).
62. Benzil *bis* - 4 - *cyclo*hexyl - thiosemicarbazone.
63. Benzil *bis* - 4 - phenyl - thiosemicarbazone.
64. Benzil *bis* - 4 - benzyl - thiosemicarbazone.
65. Benzil *bis*(4 - (2 - methylphenyl) - thiosemicarbazone.
66. Benzil *bis*(4 - (3 - methylphenyl) - thiosemicarbazone.
67. Benzil *bis*(4 - (4 - methylphenyl) - thiosemicarbazone.
68. Benzil *bis*(4 - (2 - methoxyphenyl)-thiosemicarbazone.
69. Benzil *bis*(4 - (3-methoxyphenyl) - thiosemicarbazone.
70. Benzil *bis*(4 - (4 - methoxyphenyl)-thiosemicarbazone.
71. Benzil *bis*(4 - (2 - chlorophenyl)-thiosemicarbazone.
72. Benzil *bis*(4 - (3 - chlorophenyl) - thiosemicarbazone.
73. Benzil *bis*(4 - (4 - chlorophenyl) - thiosemicarbazone.
74. Benzil *bis* - 4 - (1 - naphthyl) - thiosemicarbazone.
75. Benzil *bis* - 4 - (2 - pyridyl) - thiosemicarbazone.
76. Oxaloacetic acid thiosemicarbazone.
77. 2 - Acetyl - fluorene thiosemicarbazone.
78. Benzylidene - acetone 4 - ethyl - thiosemicarbazone.
79. Benzylidene - acetone 4 - *cyclo*hexyl-thiosemicarbazone.
80. Benzylidene - acetone 4 - benzyl - thiosemicarbazone.
81. A process for the preparation of a thiosemicarbazone as claimed in any of claims 1 to 80, in which a ketone of the general formula:—

$$\begin{matrix} X \\ Y \end{matrix}\!>\!C=O \qquad (V)$$

(wherein X and Y are as defined in claim 1) is reacted with a thiosemicarbazide of general formula:—

(VI)

$$H_2N—NH—\overset{\overset{S}{\|}}{C}—NH—R$$

(where R is as defined in claim 1) in a polar

solvent and in the presence of hydrogen ions to give the corresponding desired thiosemicarbazone of general formula I.

82. A process as claimed in claim 81, in which the ketone and the thiosemicarbazide are reacted in stoichiometric amounts.

83. A process as claimed in claim 81 or 82, in which the polar solvent employed is an alcohol.

84. A process as claimed in claim 83, in which the polar solvent employed is ethanol.

85. A process as claimed in any of claims 81 to 84, in which one of the reagents and/or the polar solvent is itself acidic and thus provides the source of hydrogen ions.

86. A process as claimed in any one of claims 81 to 84, in which a mineral acid is employed as the source of hydrogen ions.

87. A process as claimed in any of claims 81 to 86, in which the reaction is effected at elevated temperatures.

88. A process as claimed in claim 87, in which the reaction is performed at reflux of the polar solvent in which the reaction takes place.

89. A process as claimed in any of claims 81 to 88 and substantially as herein described.

90. A process as claimed in any of claims 81 to 89 and substantially as described herein with reference to any of the Examples 1 to 77.

91. A thiosemicarbazone as claimed in any of claims 1 to 80 whenever produced by a process as claimed in any of claims 81 to 90.

92. 1 - Carboethoxyamino - fluorenone and 4 - acetamido - fluorenone.

93. A process for the preparation of 1-carboethoxyamino - fluorenone or 4 - acetamido - fluorenone, substantially as herein described.

94. 1 - Carboethoxyamino - fluorenone and 4 - acetamido - fluorenone whenever prepared by any of the processes herein described.

95. A pharmaceutical composition which comprises one or more of the thiosemicarbazones claimed in claims 1 to 80 and 91, in association with a suitable pharmaceutical vehicle.

96. A pharmaceutical composition as claimed in claim 95, in which the pharmaceutical vehicle is the pulverulent solid diluent of a dusting powder or the pasty or semi-liquid oil/water or water/oil emulsion of a cream, lotion or salve.

97. A pharmaceutical composition as claimed in claim 95, in which the pharmaceutical vehicle is the ingestible excipient of a tablet, coated tablet, sublingual tablet or pill, or the ingestible container of a capsule or sachet, or the ingestible pulverulent solid carrier of a powder, or the ingestible liquid medium of a syrup, solution, suspension or elixir.

98. A pharmaceutical composition as claimed in claim 95, in which the pharmaceutical vehicle is a sterile injectable liquid solution or suspension medium.

99. A pharmaceutical composition as claimed in claim 95, in which the pharmaceutical vehicle is a base material of low melting point capable of releasing the active ingredient to perform its anti-microbial function, which base material when appropriately shaped forms a suppository or pessary.

100. A pharmaceutical composition as claimed in any of claims 95 to 99 and substantially as herein described.

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